The current situation:

Pregabalin

- Until 16th July 2017, the second-use patent remains in force for pregabalin for the treatment (where indicated) of:
  - Trigeminal neuralgia pain
  - Acute herpetic pain
  - Causalgia pain
  - (And also inflammatory, postoperative, burn, gout, and osteoarthritis pain, in the unlikely event that pregabalin is prescribed specifically to treat these types of pain)

  Lyrica® should be prescribed/supplied for these indications.

- Pfizer has stated that they will seek to have the NHS England guidance regarding generic pregabalin prescribing, issued in March 2015, (available at: https://www.england.nhs.uk/wp-content/uploads/2015/03/pregabalin-guidance.pdf) amended to reflect the Court of Appeal’s decision that Pfizer’s patent over other indications (e.g. pain except as above) was not valid.

General

- Where it is known that a second-use patent exists, the generic product should only be prescribed/supplied for non-patented indications.

PATENT INFRINGEMENT

The position is not entirely clear, but until we have a Supreme Court judgement, assume that:

- A pharmacist who applies a label to a dispensed product can infringe patent if he intentionally dispenses a generic product for a patented indication.

- A generic manufacturer is likely to infringe patent if he knows (or a reasonable person in his position would realise) that his product is likely to be used for a patented indication.

- A generic manufacturer who is selling more product than is likely to be accounted for by non-patented market share is likely to be found to be infringing patent.
Manufacturers can avoid infringing patent by taking all reasonable steps to ensure that their product is not used for patented indications. We do not currently know how far ‘all reasonable steps’ goes, and whether it includes taking a potentially infringing product off the market if all else fails, but this cannot be excluded.

DOUBLE-EFFECT

- If a doctor prescribes a generic product for a non-patented indication, and as a ‘side effect’, a condition covered by a patent is also treated/improved, the pharmacist who dispenses the prescription will not infringe the patent, as the treatment of the second (patented) condition was not intended.

  - Example: if a patient is prescribed generic pregabalin for epilepsy, but their neuralgia pain gets better, this is not patent infringement because treatment of epilepsy was intended – the improvement in the neuralgia pain was just good luck.

PREGABALIN

- Until the second-use patent runs out on 17th July 2017, the following indications for pregabalin are protected by patent:
  - Inflammatory pain
  - Postoperative pain
  - Burn pain
  - Gout pain
  - Osteoarthritis pain
  - Trigeminal neuralgia pain
  - Acute herpetic pain
  - Causalgia pain

- If pregabalin is prescribed with the intention to treat any of the above pain conditions, Lyrica should be prescribed until 16th July 2017.

- If a pregabalin is prescribed for a non-patented indication (e.g. epilepsy, or a type of neuropathic pain not included in the patented indication list), then a generic pregabalin product may be used, depending on the product licence (bearing in mind GMC advice on prescribing unlicensed and off-licence drugs.(1))
ANSWER: DETAIL

PATENT VS PRODUCT LICENCE

Patent deals with intellectual property, and the right of an inventor to restrict the use of his invention for a certain period. Medicine product licensing is a matter of patient safety and product quality and efficacy.

Thus, a manufacturer may obtain a product licence for a drug entity for which he does not hold a patent, provided that he does not infringe another person’s patent by doing so; and a patent-holder may not market a drug for which he holds the patent unless he also has a product licence (unless the requirements for unlicensed use are satisfied).

The evidence you need for a valid patent is different to the evidence you need in order to be granted a product licence. As stated below, for a patent to be valid, you just need enough evidence to prove that the invention that you are patenting is “plausible or credible”; to get a product licence you actually have to prove that it works (and that it is safe). Thus, for a patent, theoretical evidence or early animal studies might be enough; for a product licence for a human medicine, you need human trials.

Patent infringement is therefore a different problem to that of off-licence prescribing. Patent infringement is a wrong done to the patent-holder: someone is making use of his invention without his permission.

Off-licence prescribing is not necessarily a wrong at all: product licences exist to show that medicines are safe and effective. Prescribing a medicine that does not have a product licence for the condition being treated, or at all, is still permissible as long as there is no licensed product (with all its safety/efficacy evidence) suitable for the patient.

DRUG PATENTS AND MARKETING: THE BACKGROUND

The life-cycle of a drug/medicine is a complex one. On first discovery, the molecule itself is patented (the “basic patent”) in order to prevent competitors being able to use it. At that point, the race is on to get it onto the market as a licensed medicine, because patent protection only lasts for 20 years (though market exclusivity can be extended by up to five years if the patent-holder pays for a “supplementary protection certificate” – Warner-Lambert applied for one of these for pregabalin, which would have extended protection until 2018, but didn’t pay the fees, so it lapsed).

Data exclusivity is a further protection for pharmaceutical manufacturers, and it is to do with product licensing. It means that for a certain period (8-11 years, but the variations are beyond the scope of this document), although a drug is off-patent, any generic manufacturer seeking their own licence cannot use the data the originator used to apply for their licence. They’ve got the drug, but if they want to licence it as a medicine before data exclusivity expires, they have to do all their own trials. It’s generally cheaper and easier just to wait until data exclusivity expires, which is why the system works.

With most inventions, as soon as the inventor can make his product, he can put it on the market and take advantage of the full period of his patent protection, which gives him market exclusivity. Unfortunately, once a drug molecule has been invented, it still has to be tested, and all the while pre-clinical and clinical trials are being conducted, the time-limit on the patent is ticking away, and by the time the drug is finally given a product licence, there may be only a few years left on the patent.

This does not matter so much if a drug only does one thing. However, there is no incentive to do any further research to find new uses for a drug that is out of patent, or nearing the end of its patented period, if the researcher isn’t going to be able to profit from his research.

“Second-use patents” are a way around this problem. A patent always has to be for a new invention – but if the drug molecule has already been patented, that invention has been “done”, so it can’t be patented again.

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The way around this is to say that the invention isn’t the drug, it’s the new way of using it. If you can patent the new way of using the drug, then you still have an incentive to do the research.

The problem with that idea is that patent law specifically states that medical treatments cannot be patented. This is because it is more important for medical treatments to be available for all, than for the inventor to be protected.

Patent law gets around the problem of allowing second-use patents for drugs but not patenting medical treatments by saying that a second-use patent is a patent over the process of making the drug for a particular purpose. So in this case of pregabalin, the second-use patent (sometimes called a “Swiss-form patent” because the Swiss invented it) is for “the use of pregabalin for the preparation of a medicament for treating pain”.

It is important to note that because the patent is “for the preparation of a medicament” (which will then later be used for treating pain), it’s not a patent over a medical treatment. The “treatment” happens later, when the medicament is prescribed and administered to the patient.

<table>
<thead>
<tr>
<th>Patent</th>
<th>Expiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original “basic patent” for pregabalin molecule</td>
<td>May 2013</td>
</tr>
<tr>
<td>Data exclusivity</td>
<td>July 2014</td>
</tr>
<tr>
<td>Second-use “pain” patent</td>
<td>16th July 2017</td>
</tr>
</tbody>
</table>

The interesting time period, therefore, is between the expiry of the data exclusivity (July 2014) (when the drug and the data were freely available) and the expiry of the second-use patent (July 2017). During this period, pregabalin itself can be manufactured, licensed and sold – but only if it is not manufactured for use in preparing a medicament for the treatment of pain.

A generic medicine which is licensed for non-patented indications but not the patented ones, rather than the full range of the originator’s licence, results in what is termed a “skinny label”.

**PATENT VALIDITY: THE BASICS**

In order for a patent on an invention to be valid, it must fulfil several criteria:

1. The invention must not be “obvious”.
2. The invention has to be described clearly and completely.
3. The assertion that the invention will work must be plausible or credible. There must be reasonable grounds for making an assertion that the invention will do a thing at the time the assertion is made. If you make an assertion, and you turn out to be wrong, the patent fails.

The judge decided that in the case of pregabalin, Warner-Lambert had fallen foul of the third criterion: plausibility. Warner-Lambert claimed in its patent that pregabalin would be effective for "pain" (all types), "neuropathic pain", "cancer pain", "phantom limb pain", "idiopathic pain", and "fibromyalgia pain" and many other types of pain.

Where Warner-Lambert made their mistake was in casting their net too widely. The main type of pain they were interested in was peripheral neuropathic pain; unfortunately, their patent said ‘neuropathic pain’, which the judge decided included central neuropathic pain – and there was no evidence that pregabalin might be supposed to be effective for central neuropathic pain. Therefore, the ‘neuropathic pain’ element of the patent was ruled invalid. There were other elements that survived, or that were not challenged, but the failure of the main claim seriously reduced Warner-Lambert’s patent protection.
Note:

- An expired patent is one which was valid, but has run its course. It is enforceable during its lifetime (and if it is infringed during its lifetime, the patent-holder has up to six years to take action, so action can still be taken after expiry, for infringement that happened before expiry).
- An invalid patent is one that does not fulfil the requirements for patents, and is therefore judged not only not to exist now, but to never have existed. An invalid patent cannot be enforced.

PATENT INFRINGEMENT

There are two sorts of things that can be patented:

1. Products
2. Processes

“Swiss form” second medical use patents are considered to be a form of ‘purpose-limited’ process patents(2).

‘Process’ patents can be infringed by:(3)

- Using the process, or offering it for use, in the UK when you know (or it is obvious to a reasonable person in the circumstances) that doing so without the consent of the patent-holder would infringe the patent.
- Disposing of (or offering to do so), using, or importing any product obtained via that process, or keeping (for disposal or otherwise) any such products.
- The patent is also infringed if Person A supplies or offers to supply, in the UK, an essential means of putting the invention into effect when he knows (or it is obvious to a reasonable person in the circumstances) that what he supplies will be used to put the invention into effect in infringement of the patent.

This means that:

- If a manufacturer infringes a patent by making Drug X, then everyone who handles those packs will also infringe patent – even if they didn’t know that the patent existed.
- If Person A supplies Person B with a vital component for infringing a patent, and knows (or should know) that Person B will infringe the patent, then Person A also infringes the patent.

INFRINGING A SECOND USE (SWISS FORM) PATENT

Second use patents (like the patent for the manufacture of pregabalin for the purpose of treating…) are about manufacture for a purpose, so it’s very important to define what ‘manufacture’ means and what ‘for’ means. Otherwise, it might either make the patent useless, or might allow the patent-holder to prevent other people making products (or using processes) which are not patented.

For instance, in the case of pregabalin, it’s important that the patent-holder should be able to protect the manufacture of pregabalin for patented indications, but they shouldn’t be able to prevent other people manufacturing pregabalin for other indications. Otherwise, the second-use patent would just operate like the original patent for the molecule (which prevented everyone else making pregabalin), and would allow the patent-holder to effectively extend the patent forever by coming up with new uses.

Manufacturing for and infringement

The Court of Appeal has stated that a person manufactures for a purpose when he has that intention in mind; further, a person is regarded as intending what he knows or can reasonably foresee as the consequences of his actions. The intention will be negatived where the manufacturer has taken all reasonable steps within his power to prevent the consequences (i.e., infringement) occurring.(4)
Who can infringe?

In the Lyrica/pregabalin case, when it went to the High Court, Justice Arnold was of the opinion that:

- Only a person who manufactured could infringe the patent *de novo* (although of course anyone handling an already-infringing product would also infringe).
- Doctors, pharmacists and patients did not manufacture, therefore they could not infringe.
- However, if a manufacturer knew (or ought to know) that downstream, their product would be put to an infringing use, then the manufacturer would infringe the patent.

In the Court of Appeal, the Lords of Appeal interpreted the law differently in some respects. They agreed that only a person who manufactured could infringe the patent *de novo*, but they stated:

- Doctors could not infringe the patent because even though they would know that a particular prescription for pregabalin was for the treatment of one of the patented indications, they would not know which pregabalin product would be supplied. [Unless, of course, the doctor was a dispensing doctor, which was not considered.]
- *But* pharmacists potentially could infringe patent *de novo*, if they had the relevant intention (of dispensing a generic product to treat a patented indication) because applying a label could be regarded as the final stage of manufacture of the product.

Although the statement of the Court of Appeal that in their opinion it is possible for a pharmacist to infringe patent by applying a label is *obiter* (not part of the legally binding judgement), so was Arnold J’s statement in the High Court that pharmacists could not infringe patent by dispensing. Thus, the Court of Appeal view has greater force than the High Court view.

We will not have a solid statement on whether or not pharmacists can infringe patent *de novo* by dispensing a generic product in cases where the pharmacist is aware that it is prescribed to treat a patented indication until we have a court judgement where this was one of the main questions to be decided. However, it seems likely that lower courts (e.g. the High Court) will follow the Court of Appeal judgement unless there are powerful arguments to the contrary (or the Supreme Court, when the pregabalin case is heard, provides a different opinion).

Thus:

- It should be regarded as possible for a pharmacist to infringe patent by dispensing generic product when they know it for a patented indication;
- If a generic manufacturer knows that his product is likely to be used for a patented indication, he will infringe patent unless he takes *all reasonable steps* to prevent it.

AVOIDING INFRINGEMENT & IMPLICATIONS OF MARKET SHARE

In order to avoid infringement of a second-use patent, if a manufacturer foresees that his product may be used for the patented indication, he needs to take *all reasonable steps within his power to prevent the consequences occurring*. If a generics manufacturer takes ‘all reasonable steps within his power’, and such use still happens, the Court of Appeal has stated that the use of the generic product for patented indications, although foreseen, would not be ‘intended’.

The Court of Appeal did not cover quantity of potentially infringing sales: Arnold J was of the opinion that use *de minimis* (i.e., too small to be relevant) would not count. However, in some circumstances, the non-patented indication is a minor or rare one, but most of the market is for the patented indication(s). This is the case with pregabalin, as the majority of the pregabalin market is for neuropathic pain. A starker example is that of zoledronic acid, which is used for both Paget’s disease (rare) and osteoporosis (common); only a very small percentage of the zoledronic acid market is for (unpatented) Paget’s disease. The majority of the rest is osteoporosis.

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Discussion of market share occurred in the pregabalin litigation; a generic manufacturer's projections of expected market share, or their actual sales, can be used as evidence of their 'intentions'. (5) Essentially, if a generics manufacturer is aware that the non-patented indication is only 30% of the market for the drug, and they are aiming for, or achieve, a market share of more than that, then they can be assumed to know that their product is being used for the patented indication. Unless they take all possible steps to stop this, then they will be assumed to intend it.

This was the basis of the Novartis v Sun (6) litigation in the Netherlands, regarding zoledronic acid. Zoledronic acid for the treatment of osteoporosis is still under patent, but zoledronic acid for the treatment of Paget's disease is not. Sun Pharmaceuticals accepted a contract with a Dutch health insurer to be the exclusive supplier of zoledronic acid; thus, Sun Pharmaceuticals' product, which was not licensed for the treatment of osteoporosis, was supplied for all indications. Despite the fact that Sun had sent a letter to various parties informing them that their product was not licensed for the treatment of osteoporosis, the court was of the opinion that these letters were 'toothless', as Sun did nothing further. The amount of sales of Sun's product were such that Sun could not reasonably attribute them to the non-patented indication alone, so Sun must have known that their product was being used for the patented indication. Thus, Sun was liable for patent infringement.

Although this Dutch case is not binding on English courts, it does share a common theme with the pregabalin litigation: just telling people not to prescribe a generic product for a patented indication is not likely to be regarded as sufficient to avoid patent infringement – particularly when there is objective evidence that people are using the product in such a way.

Generic manufacturers are required to take all reasonable steps to prevent their product being used for the patented indications; although exactly what this might be has not been defined, it seems anything that allows significant use of the generic product for patented indications is not going to be regarded as sufficient. Justice Arnold was of the opinion that de minimis use of the generic for patented indication was probably unavoidable,(5) any situation where the generic made significant inroads into the patented market share would likely be regarded as infringement.

In practice, this means that it continues to be important to use the correct product for the correct indication. It is recognised to be inevitable that there may be a minimal amount of generic product used for the patented indication, either through patient factors (if there is a difference in formulation) or mistake, or non-availability at the time of the correct product. However, significant use is likely to be regarded as infringing patent.

It is not clear what might happen if the generic manufacturer takes all reasonable steps short of withdrawing his product from the market and still cannot prevent the use of his product for the patented indication. We do not know whether withdrawal of the product from the market would be regarded as a `reasonable step', but we cannot exclude that possibility.

Furthermore, following the Court of Appeal judgement, there is now the potential for pharmacists to be regarded as infringing patent themselves if they supply (with a label) the generic product for a patented indication. Needless to say, this is to be avoided.

DOUBLE EFFECT

The Court of Appeal has made it clear that what is intended by the word 'intent' to treat : (4)

"Intentional use is to be distinguished from use where the drug is prescribed for a different indication and, without it in any sense being the intention of the treatment, a pain condition is in fact treated." Thus, unsurprisingly in the present judgment, Floyd LJ thought that "the judge [Arnold J] fell into error in seeking to dissect the requirement for intentional treatment of pain in this way". Instead, for a Swiss form claim to be infringed "it is only essential that the manufacturer is able to foresee that there will be intentional use for the new medical indication" (where "intentional use" has the meaning just stated).
This is important in practice, as it means that if doctor prescribes generic pregabalin for a non-patented indication (e.g. epilepsy), and the generic product is supplied by the pharmacist, patent infringement does not occur even if the patient’s co-existing trigeminal neuralgia pain also happens to get better. The ‘intent’ was to treat the epilepsy, not the pain, and it is the intent that counts.

**PREGABALIN PATENT CLAIMS AND THEIR FATE**

A patent will often make multiple claims. Large, wide claims will be made first, and then progressively narrower claims. To understand this strategy, it often helps to visualise each claim as a fence enclosing a certain amount of ground. Large claims contain a lot of field; each large claim will probably have one or more smaller fenced areas (claims) inside it. When a patent claim is challenged, it will either stand or fall: if it falls, the fence for that claim is removed. If one of the larger fences is removed, then the smaller fences will remain standing, and will still protect some parts of the field.

In the case of pregabalin, the following types of pain are still patent protected:
- Inflammatory pain
- Postoperative pain
- Burn pain
- Gout pain
- Osteoarthritis pain
- Trigeminal neuralgia pain
- Acute herpetic pain
- Causalgia pain

Therefore, a patient with neuropathic pain may in general be treated with a generic pregabalin product, except if that pain is one of the narrower patented forms, e.g. trigeminal neuralgia pain.

See also ‘Double Effect’ section above.

Warner-Lambert has been granted permission to appeal to the Supreme Court regarding the pregabalin case. Currently, we do not know when the appeal will be heard.

**FINDING OUT ABOUT SECOND-USE PATENTS**

Arnold J(5) suggested that the best solution for avoiding future patent infringement in the case of second-use patents was for prescribers to write prescriptions for non-patented uses as the INN (e.g. pregabalin), and for patented uses as the correct product brand-name (e.g. Lyrica®).

He recommended that a scheme be set up whereby manufacturers wishing to protect a second-use patent should inform NHS England and the devolved governments, who could then produce guidance, as it is not reasonable to expect NHS England etc., let alone individual healthcare professionals, to keep track of everybody’s second-use patents. Generic manufacturers who wish to market products with “skinny labels” should also co-operate with NHS England and the devolved governments.

The primary value of such a system would be to protect the ability of generics manufacturers to carry on marketing products under “skinny labels” where a second-use patent exists, as the ability to manufacture generics without patent infringement hinges on the generics manufacturer’s efforts to ensure that their product would be very unlikely to be prescribed for the patented use.

Prescribers should therefore follow the GMC’s guidance(1) on prescribing unlicensed/off-licence medicines:

You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.

In the case of "skinny labels", following the GMC guidance (coupled with prescribing by brand name where patent protection exists) would result in the licensed product being supplied in the overwhelming majority of situations, and any off-label prescribing due to patient factors – such as intolerance to an excipient in the patent-holder’s product but not the generic – would likely be too few to be relevant in the consideration of patent infringement by the manufacturer.

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REFERENCES


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